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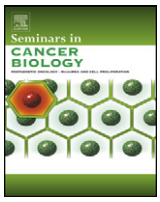

Editorial

Why systems biology and cancer?

During the 2007 meeting of the International Society for the History, Philosophy, and Social Studies of Biology that took place in Exeter, UK, one of us chaired a session entitled "SYSTEMS BIOLOGY: Who is trying to hijack it". An implication of this title was that somebody, or somebodies, were interested in owning it and taking it away as a franchise to be exploited to their benefit. Our perception then was that the gigantic effort to sequence all of the different genomes and the explosion of all kinds of "omics" were going to fall short in providing a comprehensive explanation of what the living state was about. In anticipation of this shortfall, efforts to take Systems Biology down a rational and fruitful path toward the integration of a multidisciplinary, multi-hierarchical level of analysis that eventually would explain the living state, would be delayed. Our concerns were misplaced at least from the point of view that a solid, unified consensus would be rapidly formed and that once the train left the station, it would be difficult to get on. Today, we believe that the train is still safely parked on its platform waiting for passengers to board.

From what we are witnessing, Systems Biology remains as a somewhat nebulous idea in search of the integrative effort referred to above. In a sense, it seems as if Systems Biology has forgotten its roots in the Vienna School of the pre-WWII era where the emphasis was on the whole organism: the system could not be understood by investigating it solely at the molecular level. Manfred Drack and Olaf Wolkenhauer focus their analysis on the ideas elaborated by Paul A. Weiss and Ludwig von Bertalanffy, and compare their views on Systems Biology with the approaches taken by modern practitioners of the discipline, which for the most part are bottom-up and are concerned with the dynamics of molecular interactions while disregarding additional levels of organization from their analysis. They propose that "bringing together the early heuristics with experiments and formalisms of recent systems biology is therefore an important task for the future."

Through a complementary approach, Bernd Rosslenbroich expanded on the historical and epistemological aspects of Systems Biology while emphasizing the need to apply an organicist view based on the integration of the systems approach of Paul Weiss, the developmental systems theory and the theory of increasing autonomy in evolution. From the combined analysis of these two contributions, it is apparent that efforts to reconcile modern Systems Biology with the aims of its founders will require a long-term intellectual and experimental research investment before tangible fruits materialize. Central to this anticipated success is the realization that multidisciplinary approaches and reliable premises need to be adopted, and that everyone's effort will be welcomed to finally enunciate a theory of organisms.

Acquiring a comprehensive understanding of normal developmental biology is necessary to translate such knowledge into meaningful explanations of pathological states and into ways to either prevent them or treat them. It is therefore not capriciously that Systems Biology *and* Cancer have been the focus of reviews in several biology periodicals (Cell, Science, Progress in Biophysics and Molecular Biology, and this one in Seminars in Cancer Biology). The editors and the contributors of those issues have correctly identified cancer as the pathological state *par excellence* that can be advantageously compared with normal development. Indeed, a consensus is being reached for considering cancer as development gone awry.

In 2005, the philosophers O'Malley and Dupre identified two streams within Systems Biology. The first, called 'pragmatic systems biology' emphasizes the use of large-scale molecular interactions [1]. Rexxi D. Prasasya et al. illustrate this approach by applying mathematical modeling to translate high-throughput data into signaling networks to model "how cells make decisions based on the information flow through this network" and thus find treatment targets. The other stream identified by O'Malley and Dupre, defined as 'systems-theoretic biology', emphasizes system principles. This latter stream posits that *ad-hoc* approaches are insufficient and propose instead to take into consideration emergent properties and highlight the need for a theoretical approach.

O'Malley and Dupre concluded that both varieties of Systems Biology have yet to produce a "clear account of what biological systems are"; this means that the philosophical underpinnings of their practice have neither been stated nor addressed. Indeed, a main epistemological issue to be dealt with is whether or not a mechanicist and reductionist view, totally committed to the bottom-up strategy that still dominates the thought and practice of mainstream biologists, may yield a comprehensive understanding of complex phenomena, such as cancer.

The leaning of cancer research into Systems Biology represents a tacit admission of what appears now as obvious. Namely, that a paradigmatic switch is in the making as a result of the explanatory failure of a century of unproductive concentration on premises such as that cancer is a *cell-based* disease and that proliferative quiescence is the default state of cells in metazoans: these are the premises of the Somatic Mutation Theory of carcinogenesis (SMT) [2]. For epistemic and pragmatic reasons (the latter mostly of the sociological flavor), replacing the prevalent SMT will require us to overcome the inertial realities of how the sizable cancer research enterprise is managed in the first decades of the 21st century.

Experimental evidence favoring the Tissue Organization Field Theory of carcinogenesis (TOFT) has already been collected while relying on premises diametrically opposed to those of the SMT. Objectively, the TOFT assumes that (i) *proliferation* is the default state of all cells and that (ii) cancer is a *tissue-based* disease [3,4]. As a result of the co-existence of the SMT and the TOFT, both aimed

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at explaining the same phenomenon, cancer research is traversing what Baker et al. call a period of "paradigm instability" [5]. The outcome of this theoretical competition remains unpredictable. Choosing sides at early stages of a debate requires taking risks. Most scientists, as most human beings, are reluctant to take those risks until they are convinced of the benefits of doing so. Nevertheless, a few papers that fit into the third stage of truly paradigmatic switches ("we knew it all along") are already making their way into the literature. A series of publications confirm and extend with luxuriously elegant details the power of the mammary gland microenvironment to normalize the neoplastic phenotype. Previous studies have shown that the mammary gland stroma could induce mammary carcinoma cells to form normal ductal structures [6]; the new publications confirm and extend that normal mammary epithelial cells could re-direct cancer cells of diverse origins into forming normal mammary epithelial structures when co-implanted into mammary gland stroma [7,8]. And, a recent publication also confirms that carcinogens need not directly affect the genetic material in order to elicit a neoplasia [9], and that the crucial target of carcinogens is the stroma [3,10]. Thus, the tide is turning regarding the niche where carcinogenesis begins. What it is still being ignored is the second premise of the TOFT, that is, that *proliferation* is the default state of *all* cells. This conceptual switch is likely to have a wider impact in the fields of developmental biology at large and cancer in particular.

The options offered to researchers by the two opposing stances regarding Systems Biology are both epistemological as well as methodological. While most bench biologists pay little or no attention to philosophical issues, many of them flippantly use the term "mechanistic" as opposed to "descriptive" when addressing research approaches. In this regard, Mayr remarked that researchers "tend to refer to the approach of their opponents in terms that are unflattering if not derogatory [11]." Namely, "my" research is mechanistic, "yours" is descriptive. Most biologists believe that mechanisms provide explanations at the molecular level while, epistemologically, a mechanism is a type of explanation by means of a causal chain [12]. For the most part, in the narrative of molecular biologists, a "mechanistic" approach refers to descriptions involving molecules, and not to a causal chain. Hence, as long as descriptions and correlations invoke molecules, preferably so if they are macromolecules of the nucleic acid variety, their brand of descriptive research is fine with them. What most molecular biologists appear to abhor are descriptions at higher hierarchical levels, and even high level causal chains, which epistemologically speaking are mechanisms. For example, the workings of a joint can be easily explained in terms of mechanics, without a need to refer to molecules, to the point that every day, throughout the world, thousands of hips are replaced with man-made prostheses. Similarly, complex phenomena such as organogenesis and carcinogenesis take place at higher levels of biological organization than the subcellular level on which reductionists have concentrated. In those complex phenomena, causality runs not only from the bottom-up, but also top-down. A good example of this type of causality was provided by the fact that the construction of a mathematical model for the understanding of the generation and propagation of the heart rhythm required a multi-scale approach that included the gross anatomy of the heart, without which the model did not work properly [13].

The cell-based approach to resolving the cancer puzzle aims at reaching the lowest structural "bottom" suspected to store those elusive answers. Since Crick's enunciation of the "central dogma [14]," in the view of molecular biologists, DNA has been the depository of this privileged causal power. This bottom-up approach has provided a refined catalogue of the molecular anatomy of what is inside a cell and how and when those molecules interact. Attempts to place these molecular interactions through elaborate but necessarily incomplete network patterns, from the bottom-up, have failed to provide a description of biological phenomena, since real space (inside the cells and among them) has been usually disregarded. Indeed, the adoption of the information paradigm expressed by the central dogma, which is linear, deprived the organism of its physicality resulting in the marginalization of the role of mechanics and electromagnetic forces in morphogenesis.

The essays by Kurt Saetzler et al. and by Mariano Bizzarri et al. address the role of mechanics in development and cancer while the one by Claudio Rossi et al. addresses electromagnetic interactions in cell communication. Saetzler et al. argue for the adoption of the organicist approach briefly outlined above, whereby both a bottom-up and top-down causality are taken into consideration when explaining biological phenomena at large, and carcinogenesis in particular. Additionally, they argue that topology, i.e., real space, plays a causal role that should be considered when modeling complex phenomena. Bizzarri et al. propose to concentrate research efforts at a mesoscopic level of organization in their approach to the understanding of cancer, while also highlighting the role of topology and its relationship to metabolism and dynamic processes. Sui Huang, while recognizing the role of supracellular phenomena, instead follows Waddington's epigenetic landscapes to propose a cell-centered approach while focusing it around an integrative concept, namely, that of the attractor states.

For a century now, it has been common to mix and match contradictory hypotheses and assign comparable weight to disparate datasets. The weight of influential biology textbooks, of peer-reviewed published data and of funding affect decisions by bench researchers who are weary of disregarding what has "worked" in the recent past when proposing and performing 'wet' experiments which are time-consuming and costly. Additionally, the premature adoption of hypotheses and performing experiments based on them may cost one's career if they do not hold up. The acceptance of a given explanation and its opposite under the notion that biology is too complex, runs against the very basis of the scientific endeavor. The objectives of science have been accurately defined by Ayala[1], and from this perspective, it is obvious that postulates, hypotheses and theories should be carefully scrutinized and even dropped when they cease to be productive [15].

Where does the promise of Systems Biology in understanding Cancer lie?

Mathematical modeling and computer simulation afford the type of boldness that is essential to getting to the core of the problem by providing new insights while showing also the blind alleys, without a premature commitment to a program of expensive and time-consuming 'wet' experiments. This exploratory role of Systems Biology may be central to breaking the habit of fixing lacks of fit with new epicycles instead of taking a bold and critical look at the premises adopted. The generation of counterintuitive *in silico* results may inspire new 'wet' research for both model validation and hypothesis testing.

Finally, an insightful comment by the famed British molecular biologist John Cairns reads "... Biology and cancer research have developed together. Invariably, at each stage, the characteristics of the cancer cell have been ascribed to some defect in whatever branch of biology happens at the time to be fashionable and exciting; today, it is molecular genetics" [16]. Now, when the merits of keeping alive the notion of a "cancer cell" have been meaningfully

[1] "(1) Science seeks to organize knowledge in a systematic way, endeavoring patterns of relationship between phenomena and processes; (2) science strives to provide explanations for the occurrence of events; and finally, (3) science proposes explanatory hypotheses that must be testable, that is, accessible to the possibility of rejection or falsification" (Ayala FJ. Biology as an autonomous science. Am Sci 1968;56:207–221).

challenged [17], organicism and Systems Biology could advantageously replace molecular genetics as the "fashionable and exciting branches of biology" that cancer research should rely on to resolve the cancer puzzle. Amen. . .

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